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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/923,515	08/07/2001	Rosanne M. Crooke	ISPH-0595	1714

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/923,515	CROOKE ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,7,9-13 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,7,9-13 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *March 3, 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicants Amendment and Remarks filed March 3, 2005.

Claims 2, 4, 6, 8, and 14 have been canceled. Claims 1, 5, 7, and 9-12 have been amended.

Claims 1, 5, 7, 9-13, and 15 are pending in the instant application.

Claims 1, 5, 7, 9-13, and 15 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

Applicant's information disclosure statement, filed March 3, 2005 is acknowledged. The information referred to therein has been considered on the merits.

Claim Rejections - 35 USC § 102

In the previous Office Action mailed November 3, 2004, claims 1, 5, 7, 9-13, and 15 were rejected under 35 U.S.C. 102(b) as being anticipated by Bennett et al. [U.S. Patent No. 6,008,344]. **This rejection is withdrawn** against claims 1, 5, 7, 9, 10, 12, 13, and 15 in view of Applicants amendment to the claims. Specifically, the Examiner is withdrawing this rejection in view of Applicants amendment to recite "100% complementary". It is noted that the antisense oligonucleotide disclosed by Bennett et

al. is not 100% complementary to a nucleic acid encoding SEQ ID NO:3. **However, this rejection is maintained** against claim 11 for the reasons of record set forth in the Office Action mailed November 3, 2004.

It is noted that claim 11 is drawn to an antisense compound 12 to 30 nucleobases in length targeted and 100% complementary to at least an 8-nucleobase portion of an active site of SEQ ID NO:3, wherein said compound specifically hybridizes with said active site and comprises specific modifications.

The modified antisense oligonucleotide disclosed by Bennett et al. is 100% complementary to at least an 8-nucleobase portion of an active site of SEQ ID NO:3. For example, see the sequence alignment provided in the Office Action mailed November 3, 2004. The modified antisense oligonucleotide disclosed by Bennett et al. is 100% complementary to a 10-nucleobase portion, specifically nucleobases 464-473 of SEQ ID NO:3 of the instant invention.

Therefore, Bennett et al. anticipate the claim 11.

Response to Arguments

In response to this rejection, Applicants argue that the claims have been amended to recite "100% complementary". Applicants contend that the modified antisense oligonucleotide disclosed by Bennett et al. is not contiguous and thus does not anticipate the instant claims.

This argument has been fully considered, but is not found persuasive against claim 11 because as discussed above, claim 11 is drawn to an antisense compound 12

to 30 nucleobases in length targeted and 100% complementary to at least an 8-nucleobase portion of an active site of SEQ ID NO:3, wherein said compound specifically hybridizes with said active site and comprises specific modifications. Bennett et al. disclose a modified antisense oligonucleotide that is 100% complementary to a 10-nucleobase portion, specifically nucleobases 464-473 of SEQ ID NO:3 of the instant invention.

Therefore, Bennett et al. anticipate the claim 11.

In the previous Office Action mailed November 3, 2004, claims 1, 2, 11, 12, and 14 were rejected under 35 U.S.C. 102(b) as being anticipated by Baker et al. [U.S. Patent No. 6,080,580]. **This rejection is withdrawn** in view of Applicants amendment to recite "100% complementary". It is noted that the PCR primer disclosed by Baker et al. is not 100% complementary to a nucleic acid encoding SEQ ID NO:3.

In the previous Office Action mailed November 3, 2004, claims 1, 2, 11, 12, and 14 were rejected under 35 U.S.C. 102(b) as being anticipated by McLean et al. Nature, 1987 Vol. 330:132-137. **This rejection is withdrawn** in view of Applicants amendment to recite specific modifications. It is noted that the oligonucleotide probe disclosed by McLean et al. does not comprise any modifications.

Claim Rejections - 35 USC § 103

In the previous Office Action mailed November 3, 2004, claims 1, 5, 7, 9-13, and 15 were rejected under 35 U.S.C. 103(a) as being unpatentable over McLean et al. Nature, 1987 Vol. 330:132-137, in view of Morishita et al. (Circulation, 1998 Vol. 98:1898-1904), and Baracchini et al. [U.S. Patent No. 5,801,154], and McKay et al. [U.S. Patent No. 6,258,601]. **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed November 3, 2004.

Response to Arguments

In response to this rejection, Applicants argue that McLean in combination with the generic secondary reference does not suggest desirability of the invention of Applicants claims, as now amended. Specifically, Applicants argue that the combination of McLean's disclosure of the known sequence of Apo (a) with Morishita's 43-mer ribozymes, and the general teachings of Baracchini and McKay does not suggest the modified 12 to 30 nucleobase antisense oligonucleotide of the present invention. More specifically, Applicants argue that no combination of the probe of McLean with the secondary references suggests the modified antisense compounds of the present invention that are targeted and l00% complementary to a nucleic acid molecule encoding Apo (a).

Applicants argue that Morishita is directed only to ribozymes and to a DNA oligonucleotide that are each about 42 nucleobases in length, and is therefore an

ineffective reference because it does not meet all the structural requirements of the claims, and it teaches away from antisense. While Applicants acknowledge that their specification at page 11 states, "antisense compounds include ribozymes". However, Applicants contend that one of skill in the art would readily recognize that this statement would not include antisense compounds that are less than 40 nucleobases in length, as taught by Morishita. Applicants argue that McLean only provides a reference to a probe of Apo(a), which probe does not meet the modification requirements of the claims. Applicants further argue that Baracchini and McKay cannot be combined with McLean and Morishita since these secondary references refer to targets that are not related to Apo(a). Applicants contend that there is nothing in Baracchini or McKay that assist in overcoming the negative teaching in Morishita about the use of antisense strategies applied to Apo(a).

These arguments have been fully considered, but are not found persuasive. Applicant argues against the cited references individually, but must consider the rejection based upon the combination of the references. *See*, MPEP 2145, section IV. While the ribozymes taught by Morishita et al. do not meet the structural limitations of the claims, they clearly provide motivation to make antisense oligonucleotide inhibitors to Apo(a). For example, the instant specification at page 11, lines 33-35, discloses that "antisense compounds are antisense oligonucleotides"... and "antisense compounds include ribozymes"... thus it would be obvious to one of ordinary skill in the art to interchange the ribozymes taught by Morishita et al. with the antisense compounds of the instant invention. The McLean reference was relied upon to teach the known

sequence of Apo(a). It is the Examiner's position that with this known sequence, one skilled in the art would have been motivated to make antisense oligonucleotide inhibitors targeting Apo(a) using the motivation of Morishita. Applicants argue that McLean provides a reference to a probe corresponding to the sequence of Apo(a), however, this statement is irrelevant to the instant rejection. In fact, nowhere in this rejection does the Examiner acknowledge the probe taught by McLean. Applicants contend that Baracchini and McKay cannot be combined with McLean and Morishita since these secondary references refer to targets that are not related to Apo(a). This is not found persuasive because Baracchini was relied upon to teach the motivation to make a specific length of an oligonucleotide and Baracchini was further relied upon to provide motivation for modifying an oligonucleotide. McKay teaches "antisense include ribozymes" and was thus relied upon to teach that antisense oligonucleotides and ribozymes are art-recognized functional equivalents of each other.

Therefore, one skilled in the art would have been motivated to make an antisense oligonucleotides targeted to a nucleic acid encoding apolipoprotein (a) using the sequence taught by McLean et al. and the motivation of Morishita et al. One of ordinary skill in the art would be motivated to make such antisense of a length within the range of 12 to 30 nucleotides for ease of synthesis and delivery and because it is conventional in the art to make antisense within this size range (as exemplified by Baracchini et al.). One of ordinary sill would have been motivated to incorporate modifications into the antisense oligonucleotide for the benefits of stability and improved hybridization as taught by Baracchini et al.

Therefore, the invention of claims 1, 5, 7, 9-13, and 15 would have been obvious to one of ordinary skill in the art, as a whole, at the time the instant invention was made.

Applicant's amendment necessitated the new ground(s) of rejection presented below:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5, 9, 11, 12, 13, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over McLean et al. in view of either Prosnyak et al. (Genomics, 1994 Vol. 3:490-494) or Deverre et al. (Nucleic Acids Research 1997 Vol. 25:3584-3589).

Claim 1 is drawn to a modified antisense oligonucleotide 12 to 30 nucleobases in length targeted and 100% complementary to a nucleic acid molecule encoding human apolipoprotein (a) (SEQ ID NO:3), wherein said nucleic acid molecule inhibits the expression of human apolipoprotein (a).

McLean et al. disclose a synthetic 30-base oligonucleotide probe that spanned the breakpoint of apo(a) and plasminogen similarity in the signal peptide region (see Figure 1b at dotted underline). This synthetic oligonucleotide is reverse complementary to bases 80-109 of SEQ ID NO:3 of the instant invention. It is noted that the reverse

complimentarity between the synthetic oligonucleotide disclosed by McLean et al. and nucleobases 80-109 of SEQ ID NO:3 is contiguous. Given this high degree of similarity, the synthetic oligonucleotide disclosed by McLean et al. meets the structural limitations of the claimed invention and would be expected to "specifically hybridize" with a nucleic acid molecule encoding human apolipoprotein (a) as defined in the instant specification at page 8, lines 31-35 and page 9, lines 1-13. McLean et al. do not teach modifying the probe.

Prosnyak et al. teach oligonucleotides containing 5-methylcytosine modifications as hybridization probes for DNA fingerprinting (see Abstract). Prosnyak et al. teach that 5-methylcytosine modifications increase duplex stability and improve the sensitivity of hybridization compared to unmodified counterparts (see page 490, second column).

Deverre et al. teach oligonucleotides containing phosphorothioate modifications as probes for enzyme competitive hybridization assays (see Abstract). Deverre et al. teach phosphorothioate modifications provide nuclease resistance.

It would have been obvious to one of ordinary skill in the art at the time of filing to make an oligonucleotide 12 to 30 nucleobases in length targeted and 100% complementary to a nucleic acid molecule encoding human apolipoprotein (a) (SEQ ID NO:3) to use as a sequence probe for cloning human apolipoprotein (a) as taught by McLean et al. One of ordinary skill in the art would have been motivated to modify the probe to promote tighter binding of the target, improve the sensitivity of hybridization, and protect from nuclease resistance as taught by Prosnyak et al. and Deverre et al.

Therefore, the invention would have been obvious to one of ordinary skill in the art at the time of filing.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Wang Andrew can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
March 23, 2005

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